[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Vapor Phase Halogenation of Thiophene and 2-Methylthiophene

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Thiophene was brominated in the vapor phase at temperatures up to 750° in a flow system. It was found that the monosubstitution product changes from 2-bromo- to 3-bromothiophene as the temperature rises. At 750° the monobromo product was pure 3-bromothiophene; however, the yield was only 16%. It was shown that the 3-compound does not arise through the thermal rearrangement of the 2-compound. Chlorination was carried out in the same manner at temperatures up to 600°. The transition to 3-substitution began at a lower temperature but due to heavy carbonization the temperature could not be increased sufficiently to obtain pure 3-chlorothiophene. 2-Methylthiophene was brominated in the vapor phase at 200, 400 and 600°. At 200° there was no reaction. At 400 and 600° the only brominated product was thenyl bromide. No nuclear halogenation was found.

There are still a number of relatively simple derivatives of thiophene which are either unknown or require lengthy preparative procedures. One such compound is 3-bromothiophene which is usually prepared from thiophene by a five-step method with 2-thenoic acid as an intermediate. The steps are simple and the yields are all good so the compound is available; but a method requiring fewer steps, even if more complex, would be an aid in the use of this compound in synthesis. 3-Chlorothiophene is in an analogous situation. This research was directed toward the preparation of these compounds by an entirely different approach.

The simple ionic substitution reactions of thiophene are known to proceed by way of 2-substitution almost exclusively. In a few reactions there is a small amount of the corresponding 3-isomer formed, but the amount is seldom significant and even then it is never a preparative method for the 3-compound. In halogenation there is very little of the 3-compound formed. Hartough[1] was able to detect only about 0.3% of 3-chlorothiophene in his sample of chlorothiophene prepared by direct chlorination.

During the last 20 years Wibaut and his coworkers have investigated the effect of high temperatures on the halogenation of simple aromatic and heterocyclic compounds. In many instances a change in the orientation of the substituting halogen was observed as the temperature rose. The most striking example they found was the bromination of pyridine[2] where, using a flow system, it was possible to obtain 3-bromopyridine at 300° reaction temperature but 2-bromopyridine at 500°. Use of cuprous bromide catalyst made it possible to obtain 2-bromopyridine at 300°. This change in the orientation with temperature was found to a varying extent in a number of compounds.

Since it is well known that thiophene is very resistant to heat it was decided to study its bromination in the vapor phase. There is no record of any previous attempts to halogenate thiophene at temperatures above its boiling point.

The chief difference between pyridine and thiophene in these reactions is that the former resists halogenation while the latter is readily attacked at room temperature. It was hoped that the high dilution conditions of the vapor phase would help to overcome any tendency to polybromination at the higher temperatures. This was realized in practice. Thiophene also forms addition products in its reaction with halogens and, since they were not of interest in our investigations, they had to be removed or destroyed. The usual procedure for this was to reflux the halogenation product with potassium hydroxide pellets for a long period. It was decided to follow this method since Hartough[1] had shown that it does not affect the amounts of 2- and 3-halothiophenes.

The apparatus employed was quite similar to that described by den Hertog and Wibaut.[2] The method of carrying out the bromination, the processing and analytical details are described in the Experimental part. Temperatures ranged from 300 to 750°. Because of carbonization effects it was not practicable to go any higher. The duration of contact in the hot zone ranged from 4 seconds at 300° to 0.5 second at 750°. No packing was used in the tube. At the higher temperatures any packing would have been coated with carbonaceous material very rapidly.

The results showed that thiophene does resemble pyridine in its behavior during high temperature bromination, but the conditions necessary for the change in orientation are much more severe. The yield of 3-bromothiophene at most was 16%. The best yield was obtained at the maximum practicable rate of flow. It appears that while 3-bromothiophene can be prepared by this method, the longer method is still the preferred one.

In order to establish whether the 3-bromothiophene was formed directly at this temperature, or if 2-bromothiophene was formed first and underwent rearrangement to the 3-compound, the following experiments were carried out. A sample of pure 2-bromothiophene was passed through the tube at 750° and the product processed in the usual manner. Then, to simulate the conditions of our brominations, another sample was passed through at 750° in the presence of twice its molar quantity of dry hydrogen bromide and worked up in the same manner. In both trials there was much carbonization but analysis failed to show the presence of even a trace of 3-bromothiophene in either product. This seems to rule out any formation and rearrangement of 2-bromothiophene.

The chlorination of pyridine in the vapor phase was found by Wibaut and Nicolai[3] to show a

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[1] H. L. Coonradt, H. D. Hartough and G. C. Johnson, THIS JOURNAL, **70**, 2564 (1948).

[2] H. J. den Hertog and J. P. Wibaut, *Rec. trav. chim.*, **51**, 381 (1932).

[3] J. P. Wibaut and J. R. Nicolai, *ibid.*, **58**, 709 (1939).

similar orientation change. The transition temperature was 200° lower, however, and over a shorter temperature range than for the bromination. On this basis it was hoped that the high temperature chlorination of thiophene would yield 3-chlorothiophene at a lower temperature and with less carbonization than in the case of bromination. No previous chlorination had been carried out above the boiling point of thiophene.

Chlorination experiments were conducted between 250–600° and at contact times from 2.5 to 0.67 sec. Between 250–450° 2-chlorothiophene was formed with no more than a trace of the 3-isomer. At 550°, however, one quarter of the chlorothiophene obtained was 3-chlorothiophene, and this fraction changed to three-quarters at 600°. Extensive carbonization made impractical any experiment at 650°, but it would seem that this would be the temperature at which all the product would be the 3-isomer. Thus, the general picture with thiophene does agree with the results with pyridine in that the transition during chlorination takes place at a lower temperature than for bromination. Carbonization in the thiophene work was much heavier than in the pyridine studies.

2-Methylthiophene was also studied in these vapor phase halogenations. Wibaut has confined his investigations to unsubstituted nuclei or to compounds substituted with halogen or hydroxyl groups. Mason and his co-workers[4] have carried out the only recorded investigation of a similar compound. They chlorinated toluene at temperatures up to 700° in much the same manner as Wibaut did later with pyridine and related compounds. Their apparatus was similar but did not allow the reactants to be preheated. Their findings agree very well with our results in the bromination of 2-methylthiophene.

Opolski[5] investigated the bromination of 2-methylthiophene and found that nuclear bromination predominated even in sunlight, or in the boiling liquid. Steinkopf[6] agreed that the nucleus was completely substituted before the side chain was attacked. Their investigations, however, did not go above the boiling point of 2-methylthiophene.

A trial bromination at 200° proved to be completely non-reactive. Almost no hydrogen bromide was evolved and bromine recondensed in the receiver. In a second experiment at 400° the reaction was essentially complete. A 3:1 molar ratio of 2-methylthiophene to bromine was used, with a contact time of two seconds. The carbonization was fairly heavy but there was less than 0.1% of unreacted bromine in the product. The product had to be processed immediately since decomposition usually began within an hour. The yield of thenyl bromide was 35–42% based on the bromine consumed. At 600° two trials were made with contact times of 1.5 and 3 seconds. The conversion to thenyl bromide was about 6% each time with about 80% recovery of the methylthiophene. At both temperatures the residue was a thick black tar from which a small amount of an unidentified white solid was isolated. No evidence for nuclear halogenation was found in any trial nor did Mason find any nuclear chlorination of toluene. There was no indication of the formation of addition products in these experiments as evidenced by the fact that two methods of analysis agreed roughly, one of which was sensitive to these compounds. Also the analysis of the content of sodium hydroxide traps which washed the hydrogen bromide out of product gases indicated that all the bromine had reacted by substitution. Mason and his co-workers detected benzylidene chloride in their product, but we found no thenylidene bromide in our experiments.

Experimental

Samples of thiophene and 2-methylthiophene were supplied for this investigation by The Texas Company.

The apparatus for the high-temperature halogenations somewhat resembled that of den Hertog and Wibaut.[2] A vertical Pyrex reaction tube, 56 × 2.2 cm., was heated by an electric furnace over a length of 33 mm. It was fitted with a standard taper adapter at the bottom to deliver the products into a chilled receiver, and at the top for adding the reactants. The top attachment was in the nature of a 24/40 standard taper hollow stopper which carried a side arm delivery tube for the thiophene, and a ring-sealed through-tube of 12 mm. diameter for the bromine. The latter tube extended into the reactor tube to a depth of 8 cm. below the top of the furnace and served as a preheater before mixing of the reactants. The thiophene arm also was fitted with a side-arm tube to permit dilution with nitrogen when desired to moderate the reaction, this tube carrying a shut-off stopcock. Nitrogen was used also to flush the air from the apparatus before heating. An external thermocouple was placed so that the hot junction was opposite the point of mixing of the preheated vapors.

When the reaction tube was in place, and the open annulus at each end of the furnace was plugged with asbestos, the temperature along the heated length of the tube was quite uniform. The exact temperature inside the tube at the point of reaction was not known but the results of this arrangement were reproducible. The desired temperature was controlled by a Leeds and Northrup "Micromax" Recorder Controller connected to the thermocouple, which recorder, in turn, was connected to an anticipatory circuit, a Leeds and Northrup "Droop Corrector," which caused the furnace heater to maintain the temperature inside the furnace within a degree or two of the set value. The "Pyrex" reaction tube used at lower temperatures was replaced at 750° by a "Vycor" tube of almost the same dimensions to avoid distortion of the "Pyrex" one.

The contact time was calculated assuming that the two hot vapors were in contact from the point of mixing to the end of the furnace, a volume of 63.7 ml. A calibrated flowmeter indicated the volume of nitrogen passing through the system and the volumes of the reactants were calculated from the number of moles used.

Analysis.—Because of the small difference in the boiling points of the two bromothiophenes it seemed unlikely that they could be separated easily by fractionation since the amounts handled would be small. Of the various chemical methods available, two were used. The first method was mercuration of the monobromo fraction of product by the method of Steinkopf and Bauermeister.[7] The two bromothiophenes form characteristic derivatives with widely separated melting points; 5-bromo-2-thiophenemercuric chloride, m.p. 225°, and 3-bromo-2-thiophenemercuric chloride, m.p. 120.5–123°. It was found that when a derivative was prepared from a 1-g. sample of a mixed monobromo product the derivative of 2-bromothiophene precipitated more rapidly than that of 3-bromothiophene enabling a rough separation followed by fractional crystallization from ethanol. The yield was usually 85% or more and the weights of the derivatives enabled the percentages of the two isomers to be calculated.

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[4] J. Mason, C. A. Smale, R. N. Thompson and T. S. Wheeler, *J. Chem. Soc.*, 3150 (1931).

[5] St. Opolski, *Bull. Acad. Sci. Cracow*, 727 (1904); *J. Chem. Soc. Abstracts*, I, **88**, 367 (1905).

[6] W. Steinkopf, *Ann.*, **513**, 281 (1934).

[7] W. Steinkopf and M. Bauermeister, *Ann.*, **403**, 50 (1914); W. Steinkopf, H. Jacob and H. Penz, *ibid.*, **512**, 136 (1934).

TABLE I

BROMINATION CONDITIONS AND RESULTS

Bromination temp., °C.	Contact time, sec.	Thiophene, mole	Bromine, mole	Unreacted thiophene, g.	Bromothiophene, g. (%)[b]	Residue, g.	Analysis of monobromo fraction By mercuration, %	By nitration, %
300	4	0.50	0.375	9.2	9.0 (15)	11.8	*c*	...
500 (a)	3	.80	.50	20.4	24.0 (26)	20.9	*c*	...
(b)[a]	3	.80	.50	19.0	31.6 (30)	41.5	*c*	...
650	2	.90	.70	11.2	36.0 (35)	45.5	7–8	8[e]
700 (a)	2	.84	.78	7.0	40.2 (30)	41.2	40–45	38[f]
(b)	1.5	.84	.78	8.5	37.0 (28)	37.5	35–39	...
750 (a)	0.5	.81	.50	8.0	13.2 (16)	11.6	*d*	...
(b)	1	.68	.51	11.2	9.6 (10)	9.7	*d*	...

[a] Using blackened tube. [b] % conversion, based on thiophene consumed. [c] No evidence for more than a trace of 3-bromothiophene in the monobromo fraction. [d] No trace of the derivative of 2-bromothiophene in the products of either mercuration or nitration (f). [e] Method of Steinkopf, Jacob and Penz.[7] [f] Method of Babasinian.[8]

TABLE II

CHLORINATION CONDITIONS AND RESULTS

Chlorination temp., °C.	Contact time, sec.	Thiophene, mole	Chlorine, moles	Unreacted thiophene, g.	Chlorothiophene, g. (%)	Residue, g.	Analysis of monochloro fraction by mercuration, %
250	2.5	0.90	1.25	27.0	16.8 (25)	37.8	*a*
350	2	.90	1.25	23.0	19.5 (26)	30.0	*a*
400	1.5	.90	0.95	23.4	18.0 (24)	12.0	*a*
450	2	.90	.90	40.1	17.3 (25)	16.0	*a*
500	2	.90	.90	36.2	17.5 (32)	12.1	*b*
550	1	1.25	.60	73.5	9.1 (21)	13.1	21–27
600	0.67	1.80	.50	113.7	5.2 (10)	10.0	74

[a] No evidence for more than a trace of 3-chlorothiophene in the monochloro fraction. [b] A few per cent. of 3-chlorothiophene.

The second procedure was the nitration of the monobromo fraction of the product to the corresponding 2-nitro-5-bromothiophene, m.p. 48–49° and 3-nitro-2-bromothiophene, m.p. 81–83°. This was done by the method of Steinkopf, Jacob and Penz[7] for the first trial, but by the method of Babasinian[8] in later one. Both methods enabled a good separation of nitro derivatives and the results agreed well with those from mercuration, although the yield of product was only 55–60%.

Bromination Procedure.—Bromine and thiophene were passed through the system at the chosen temperature by dropping the liquids slowly at a rate determined by experience. The flow of nitrogen was begun during the period when the furnace was heating and was later adjusted to give a contact time of from 0.5 to 4 seconds. At higher temperatures the more rapid rate of flow was necessary. Thiophene flow was started first and stopped last to prevent any excess bromine concentration. The carbonization negligible at low temperatures, gradually increased until it was very heavy.

The product from the first trial was washed with water, dilute sodium carbonate solution and again with water. It was then dried and distilled. The slow evolution of hydrogen bromide during distillation, especially as the temperature rose above 100°, indicated that addition products were present and had not been removed by this simple washing. The procedure was then modified to destroy the addition compounds by a standard method. The product was heated 18 hours on a steam-bath with 10–15 g. of potassium hydroxide pellets. After cooling the solid was removed by filtration and washed with pentane, dried and the pentane removed. The vigorous reactions at 650° and higher yielded a product containing suspended carbonaceous material as well as blackening the walls of the tube. Dilution of the contents of the receiver caused the black solid to settle. It was removed by filtration and the clear liquid was then processed as before. Results are collected in Table I.

As a further check on the identity of the bromothiophene fraction from the 750° bromination, 2 g. was converted in the manner of Steinkopf and Petersdorff[9] to 2,5-diiodo-3-bromothiophene by means of the bis-(acetoxymercuri) and the bis-(chloromercuri) derivatives. The over-all yield was 3.3 g. (90%) of solid, m.p. 55–57° (lit. m.p. 55–56°).

Behavior of 2-Bromothiophene at 750°.—Fifty grams of 2-bromothiophene (b.p. 149–151°) was passed through the reaction tube at 750° over a period of 30 minutes with the nitrogen flow such that the contact time was about two seconds. Carbonization was quite heavy and the content of the receiver was processed in the usual manner. Recovery was 40.2 g., b.p. 149–151°. A chloromercuri derivative was prepared which melted entirely at 215–220° (lit. m.p. of 5-bromo-2-thiophenemercuric chloride 225°), and showed no evidence of even a trace of the chloromercuri derivative of 3-bromothiophene.

One-third cf a mole of bromothiophene and two-thirds of a mole of hydrogen bromide were passed through the reaction tube at 750° over 30 minutes. The nitrogen flow was such that the contact time was two seconds. The product was processed in the usual manner and fractionation gave back 80% of the starting material from which a chloromercuri derivative was made. Again there was no indication that any 3-bromothiophene had been formed under these conditions.

Chlorination.—The apparatus was modified by replacing the bromine dropping funnel with a gas inlet tube. Chlorine gas from a cylinder was passed through a calibrated manometer into the reaction tube. In later experiments where carbonization was especially heavy the chlorine was diluted with nitrogen before entering the system. Chloromercuration was again the method of analysis. The chloromercuri derivative of 2-chlorothiophene melts at 218–219° while that of 3-chlorothiophene melts at 137–138°. Once more it was possible to make a preliminary separation of derivatives due to the difference in the rates of formation. Fractional crystallization completed the separation.

The chlorinations proceeded smoothly following the method developed for brominations except that at the higher temperatures it became necessary to dilute both the reactants with nitrogen. Carbonization began at 550° and was very heavy. The processing of products was the same as for the brominations, with results shown in Table II.

Bromination of 2-Methylthiophene. Analysis.—Since the most likely product would be 2-thenyl bromide, two analytical methods were devised to determine the amount of this compound in the product. The first procedure was to dissolve a weighed sample of the crude product in 10 ml.

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[8] V. S. Babasinian, THIS JOURNAL, **57**, 1763 (1935).

[9] W. Steinkopf and H. V. Petersdorff, *Ann.*, **543**, 130 (1940).

of approximately *N* sodium methoxide in absolute methanol and reflux for an hour. After cooling and dilution with water it was made just acid with nitric acid and titrated with standard silver nitrate solution. From the amount of bromide ion, the amount of thenyl bromide in the sample and hence in the total product could be calculated.

For the second method a sample was dissolved in chloroform and a saturated solution of hexamethylenetetramine in chloroform was added. After shaking the mixture for a short time it was refluxed for an hour and cooled. The adduct was separated by filtration and dried. The weight of solid enabled the amount of thenyl bromide in the sample to be calculated; in addition, the melting point of the adduct provided a check on the identity of the compound. Finally, the adduct was steam distilled and the distillate made slightly acid and extracted with ether. After drying and removing the ether, the 2-thenaldehyde isolated was identified by its 2,4-dinitrophenylhydrazone and by its semicarbazone.

In order to determine whether any product other than thenyl bromide had been formed, a sample of the crude reaction product was refluxed with 10% aqueous potassium hydroxide for an hour and extracted with ether. After drying and removal of the ether the product was distilled. Besides unreacted 2-methylthiophene the only other volatile material was thenyl ether. This compound has been reported by Emerson and Patrick[10] as the product of the action of aqueous sodium hydroxide on thenyl chloride. They reported no derivative and gave only a sulfur analysis, but were able to crystallize the material. We were not able to crystallize our sample, but its molecular weight was determined and a chloromercuri derivative was prepared and analyzed for sulfur.

Bromination at 200°.—The reactants were 0.50 mole of 2-methylthiophene and 0.14 mole of bromine, the contact time being three seconds. It was evident that the reaction was incomplete even with this small amount of bromine. The product was pink colored and slowly gave off hydrogen bromide.

Bromination at 400°.—With the nitrogen flow adjusted to give a contact time of two seconds, the reactants added were 0.50 mole of thiophene and 0.16 mole of bromine. The condensed product was a clear yellow liquid. A small sample, 1.053 g., was analyzed for side-chain bromine by the first method. Titration required 21.0 ml. of silver nitrate solution (1.00 ml. = 8.06 mg. of bromide ion). This indicated 35% by weight thenyl bromide or a conversion of 40% on the basis of bromine consumed.

For the second method of analysis a 25-g. sample was dissolved in 150 ml. of chloroform and a saturated solution of 14 g. of hexamethylenetetramine in chloroform was added. The adduct weighed 19.0 g., m.p. 162–163°. Blicke and Burckhalter[11] reported a melting point of 160–161° (dec.) for the compound. This indicated that the product contained 42% of thenyl bromide by weight.

The contents of the sodium hydroxide traps were collected and made up to 1000 ml. A 5-ml. aliquot required 7.20 ml. of silver nitrate solution (1.00 ml. = 8.06 mg. of bromide) indicating that 11.6 g. or 0.16 equivalent of bromide was in the traps. Since the bromine added in the trial was 0.16 mole nearly all must have reacted by substitution.

The crude product weighing 34 g. from a trial at 400° was refluxed with 10% potassium hydroxide solution for one hour, cooled and extracted with ether. After drying, the ether was removed and the product distilled. Besides 17.0 g. of unreacted 2-methylthiophene, b.p. 108–113°, 7.1 g. of liquid of b.p. 94–95° (0.7 mm.) was obtained. Emerson and Patrick[10] reported the b.p. of their thenyl ether as 120–125° at 1 mm. A molecular weight by the Rast method was performed: calcd. for $C_{10}H_{10}OS_2$, 210; found, 214. A chloromercuri derivative was prepared, m.p. 180–181°.

Anal. Calcd. for $C_{10}H_8Cl_2Hg_2OS_2$: S, 9.42. Calcd. for $C_{10}H_9ClHgOS_2$: S, 14.38. Found: S, 14.18, 14.24.

From the gummy black distillation residue a white solid was obtained by vacuum sublimation which, after several crystallizations from ethanol, melted at 133–134°. The C, H analyses were performed by Mrs. C. White.

Anal. Calcd. for $C_{10}H_9S_2$ or $C_{20}H_{18}S_4$: C, 62.13; H, 4.69; S, 33.18. Calcd. for $C_{10}H_{10}S_2$: C, 61.81; H, 5.19; S, 33.00. Calcd. for $C_{15}H_{14}S_3$: C, 62.03; H, 4.86; S, 33.11. Found: C, 62.33; H, 4.73; S, 32.85, 32.78.

A molecular weight by the Rast method failed due to partial decomposition. An attempt to benzoylate by the Friedel–Crafts method led to resinous material.

Bromination at 600°.—The reactants were 0.50 mole of 2-methylthiophene and 0.35 mole of bromine. The contact time was 1.5 seconds and the addition was carried out over 20 minutes. The product was clarified by the addition of pentane followed by filtration to remove the carbonaceous material. After the pentane had been distilled the unreacted methylthiophene was recovered in 80% yield. The residue was analyzed for side chain bromine by the second method. The weight of adduct indicated that the conversion to thenyl bromide was 6% based on the methylthiophene consumed. The black residue again yielded a small amount of the unidentified solid, m.p. 133–134°.

A second trial at 600° was carried out over a period of 70 minutes using the same amounts of reactants and with the nitrogen flow such that the contact time was three seconds. The processing was done as before and the results were the same as for the more rapid trial. Again there was no evidence of any nuclear halogenation.

Investigation of Black Solid from Vapor Phase Halogenations.—In all the high temperature reactions involving thiophene a black solid was obtained as by-product in considerable quantity. It seemed of interest to investigate its properties and composition. Part was deposited on the walls of the reaction tube as a brittle film and the rest was suspended in the product liquid as an amorphous black solid.

Ciusa[12] reported the formation of a similar "graphite" from the pyrolysis of tetraiodothiophene at red heat. His compound had the formula $(C_4S)_n$, but ours did not possess any such simple formula. A quantity of the solid from the 550° chlorination of thiophene was extracted with carbon disulfide in a Soxhlet extractor for two hours, dried and analyzed. The C, H analysis was done by Miss J. Sorenson.

Anal. Found: C, 49.99; H, 1.62; Cl, 20.8; S, 23.6; ash, 1.3.

Thus the C:S ratio was 5.5:1, and some sulfur must have been lost in the pyrolysis. The solid was insoluble in all organic reagents and in concentrated sulfuric acid. It did not melt and it burned with a blue flame emitting much sulfur dioxide. The halogen could not be removed with hot concentrated base.

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(10) W. S. Emerson and T. M. Patrick, Jr., *J. Org. Chem.*, **14**, 790 (1949).

(11) F. F. Blicke and J. H. Burckhalter, THIS JOURNAL, **64**, 477 (1942).

(12) R. Ciusa, *Gazz. chim. ital.*, **52**, 130 (1922); **55**, 385 (1925); *J. Chem. Soc. Abstracts* I, **122**, 1057 (1922); I, **128**, 1083 (1925).